IN THE UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCE'S

In re application of:	Michael D. Edge
Serial No:	09/398,610
Filed:	September 17, 1999
For:	TRANSGENICALLY PRODUCED PROTEINS
Art Unit:	1632
Examiner:	Anne Marie S. Wehbe
Attorney Docket Number:	GTC-42

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Dear Sir or Madam:

This application is before the Honorable Board of Appeals on appeal from the Final Rejection issued by the Examiner dated August 15, 2002, wherein all the claims under consideration, claims 1-18, were finally rejected. A Notice of Appeal being timely filed on November 6, 2002.

Please charge the filing fee of $ 160.00 to GTC Biotherapeutics' Deposit Account No. 502092, in compliance with 37 CFR § 1.17(c). As required by 37 CFR § 1.192 this Brief is filed in triplicate. The petition for an extension of time is also attached, please charge the fee of $ 985.00 for a five-month extension of time for a small entity and any deficiencies to the GTC Biotherapeutics' Deposit Account No. 502092. Accordingly, this brief was timely filed on June 27, 2003.

On September 25, 2003 the Examiner issued a Notification of Non-Compliance with regard to the brief originally filed in this case, calling for a clarification of the Summary of the Invention. Response to this Notification is timely filed if the item of non-compliance is corrected and the brief re-filed within a one month period. 37 CFR § 1.192(c). Accordingly this brief, with a more concise explanation of the current invention, is again timely filed. The

CERTIFICATE OF MAILING BY EXPRESS MAIL

I hereby certify that under 37 CFR §1.10 that this correspondence is being deposited on October 23, 2003 with the United States Postal Service as Express Mail Post Office to Addressee with sufficient postage in an envelope addressed to: Mail Stop Appeal Brief - Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Kristin Kaberry
Kristin Kaberry

Commissioner is authorized to charge any deficiencies in payment or any necessary extensions to the GTC Biotherapeutics' Deposit Account No. 502092. Favorable action on the Appellants outstanding claims is earnestly solicited.

REQUEST FOR ORAL HEARING

An oral hearing was and remains requested in this case. Please charge the fee of $280 and any deficiencies to the Appellants' Deposit Account No. 502092.

(1) REAL PARTIES IN INTEREST

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ATTN: National Institutes of Health

This application has been assigned to Genzyme Transgenics Corporation (whose successor-in-interest is GTC Biotherapeutics, Inc.), AstraZeneca UK Limited and United States of America, as Represented by the Secretary of Health and Human Services by each Party's respective Inventor(s). The original Assignments signed by the Inventors are attached hereto as Appendix A.

(2) RELATED APPEALS AND INTERFERENCE'S

To the best of Applicant's knowledge there are no appeals or interference actions that will be affected by this appeal.

(3) STATUS OF CLAIMS

Claims 1-8, 10-14, and 16-35 are pending in the application. Claims 1-8, 10-14, and 16-35 1 remain in this case. Claim 9 was canceled and both independent claims 1 and 16 were amended by the response dated November 26, 2002, entered by the Examiner.

(4) STATUS OF AMENDMENTS

It is the Appellants understanding that the Examiner entered the amendments made in the Applicant's response dated November 26, 2002. No amendments have been filed subsequent to the Final Rejection issued by the Examiner.

(5) SUMMARY OF THE INVENTION

The current invention provides a method of making a transgenic immuno-fusion protein of interest and more specifically in the development and expression of an immunoglobulin-enzyme fusion protein in a transgenic animal platform. (See the Specification, page 19, lines 18-25; page 22 lines 10-15; page 24 lines 5-29; page 31 lines 1-29; Examples 3 & 4 starting on page 48). The method includes providing a transgenic animal, e.g., goat, cow or other animal, preferably a mammal, that can express a transgenic immunoglobulin-enzyme fusion protein of interest. The methods provided also include the purification of the immunoglobulin-fusion protein of interest from the milk of a transgenic mammal. (See the Specification, page 32, lines 2-19; page 22 lines 10-15; page 47 lines 8-24). Various elements of the invention that are also described and recited in the claims include milk specific promoters, signal sequences, DNA insertion methods and expression vectors for use in developing desired transgenic animals, particularly milk specific

promoters for production in milk. (See the Specification, page 28, lines 22-29; page 29 lines 1-30). The methods of making a transgenic animal useful in the production of proteins of interest was known at or prior to the time of filing in 1999, and was relied upon by the Applicants. (See the Specification, page 26, lines 22-29; page 27 lines 1-30; page 28 lines 22-28; and see prior art references page 59-63).

To effectuate the expression of the therapeutic fusion molecule envisioned by the invention the specification recites the use of an immunoglobulin subunit (IgG) or other targeting molecule (i.e., a first polypeptide of interest) fused to a second non-targeting polypeptide of interest. (See the Specification, page 24, lines 5-27; page 22 lines 10-15; see Example 3 starting on page 48). The first polypeptide is envisioned to include the subunit of a targeting molecule, e.g., an Ig subunit, a carcinoembryonic antigen (CEA), a transferrin receptor, an epidermal growth factor receptor or the like. The second member can be: an enzyme; a polypeptide other than an Ig subunit. (See the Specification, page 48, lines 6-29; page 50 lines 12-29; pages 51-52.)

Most preferably, the transgenic immuno-fusion protein of the invention is expressed in the mammary gland of the transgenic mammal, e.g., a ruminant and thereafter secreted into the milk of the transgenic mammal in concentrations that are sufficiently high to be commercially viable. The transgenic immuno-fusion protein of the invention is expressed under the control of a mammary gland specific promoter, e.g., a milk specific promoter such as a casein promoter. Other examples of controlling promoters include: the beta-lactoglobulin promoter, whey acid protein promoter, or lactalbumin promoter. (See the Specification, page 28, lines 21-29; page 29 lines 1-20). The complete peptide sequence of the immuno-fusion protein of interest has the formula: R1-L-R2; R2-L-R1; R2-R1; or R1 -R2, wherein R1 is an immunoglobulin or other moiety capable of targeting the expressed fusion polypeptide, L is a peptide linker and R2 is an enzyme moiety. (See the Specification, page 2, lines 27-28; page 3 lines 1-23).

To insure that the immuno-fusion protein of interest is expressed the invention contemplates the use of a signal sequence which directs the secretion of the fusion protein from the mammary epithelial cell. In preferred embodiments, the transgene encoding the transgenic fusion protein is a nucleic acid construct which includes: a) an insulator

sequence; b) a promoter, (e.g., a mammary epithelial cell specific promoter); c) a nucleotide sequence which encodes a signal sequence which can direct the secretion of the fusion protein, e.g. a signal from a milk specific protein; d) a nucleotide sequence which encodes a sufficient portion of the amino terminal coding region of a secreted protein, e.g. a protein secreted into milk, to allow secretion, e.g., in the milk of a transgenic mammal, of the non-secreted protein; e) one or more nucleotide sequences which encode the immuno-fusion protein, e.g., an immunoglobulin-enzyme fusion protein, (e.g., a protein as recited in the claims); and f) a 3' untranslated region from a mammalian gene, e.g., a mammary epithelial specific gene, (e.g., a milk protein gene). (See the Specification, pages 30-31 and the claims as drafted pages 65-66).

In preferred embodiments, the transgenic animal is a mammal, and the immunoglobulin-enzyme fusion protein is secreted into the milk of the transgenic animal at concentrations of at least about 0.1 mg/ml, 0.5 mg/ml, 1.0 mg/ml, 1.5 mg/ml, 2 mg/ml, 3 mg/mi, 5 mg/ml or higher. (See the Specification, page 2, lines 20-23; figures 2A and 2B; page 58 lines 27-28).

A "transgenic animal", as used herein, refers to a transgenic non-human animal in which one or more, and preferably essentially all, of the cells of the animal contain a transgene introduced by way of human intervention, such as by transgenic techniques known in the art. (Specification pages 54-57). The transgene can be introduced into the cell, directly or indirectly by introduction into a precursor of the cell, by way of deliberate genetic manipulation, such as by microinjection, nuclear transfer or by infection with a recombinant virus. (See the Specification, page 26, lines 21-27; page 27 lines 9-30; page 28, lines 5-17). Mammals, for the purposes of the current claims, are defined as all animals, excluding humans that have mammary glands and produce milk.

References Relied Upon or Made of Record by the Examiner

a) Rybak SM *et al.*, *Humanization of Immunotoxin,* PROC. NAT'L ACAD. SCI. (USA) (1992); Apr 15; 89(8):3165-9.

b) Hyttinen et al., United States Patent 5,959,171, *Method For The Production Of Biologically Active Polypeptides In A Mammal's Milk*, Issued: September 28, 1999, Filed: August 17, 1994.

References Made of Record or Documents Relied Upon by the Appellants

a) Rybak SM *et al.*, *Humanization of Immunotoxin,* PROC. NAT'L ACAD. SCI. (USA) (1992); Apr 15; 89(8):3165-9.

b) Hyttinen et al., United States Patent 5,959,171, *Method For The Production Of Biologically Active Polypeptides In A Mammal's Milk*, Issued: September 28, 1999, Filed: August 17, 1994.

c) Frankel AE, et al., "Anthrax fusion protein therapy of cancer" CURR PROTEIN PEPT SCI. 2002 Aug;3(4):399-407.

d) Nagy ZA, et al., "*Fully human, HLA-DR-specific monoclonal antibodies efficiently induce programmed death of malignant lymphoid cells*" NAT MED. 2002 Aug;8(8):801-7.

e) R Harmon, **PATENTS AND THE FEDERAL CIRCUIT** § 2.3(b) (3d ed. 1994).

Case Law Made of Record, or Relied Upon by Appellants

a) In re Bell, 991 F.2d. 781, 26 U.S.P.Q. 1529 (Fed. Cir. 1993).

b) Carella v. Starlight Archery, 231 U.S.P.Q. 644 (Fed. Cir. 1986).

c) Cuno Eng'g Corp. v. Automatic Devices Corp., 314 U.S. 84, at 91 (1941).

d) In re Clay, 23 U.S.P.Q. 2d 1058, 1060 (Fed. Cir. 1992).

e) In re Dillon, 919 F.2d at 696, 16 USPQ2d at 1904 (Fed. Cir. 1990) (*en banc*).

f) In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

g) In re Geiger, 815 F.2d 686, 2 USPQ2d 1276, 1278 (Fed. Cir.1987).

h) Graham v. John Deere Company, 383 U.S. 1, (1966).

i) King Instrument Corp. v. Otari Corp., 226 U.S.P.Q. 402, 405 (Fed. Cir. 1985).

j) In re Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

k) In re Rijckaert, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993).

l) United States v. Adams, 383 U.S. 39 at 49-51 (1966).

m) Union Carbide Corp. v. American Can Co., 220 U.S.P.Q. 584, 588 (Fed. Cir. 1984).

n) Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 1054-55 (Fed. Cir. 1988).

o) Wang Laboratories, Inc. v. Toshiba Corp. 26 U.S.P.Q. 2d 1767, 1773 (Fed. Cir. 1993).

p) In re Wilder, 429 F.2d 447, 166 U.S.P.Q. 545 at 548 (C.C.P.A. 1970).

q) W.L. Gore & Assocs. v. Garlock, Inc., 721 F.2d 1540, 1549-50 (Fed. Cir. 1983).

r) Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc. 231 F.3d 1339; 56 U.S.P.Q.2D 1641 (Fed. Cir. 2000).

(6) ISSUE

The Board must decide:

I. Are claims 1-8, 10-14 and 16-35 allowable under 35 U.S.C. §103(a) over United States Patent No.# 5,959,171 to Hyttinen *et al.*, in view of Rybak *et al.*, " *Humanization of Immunotoxins*", PROC. NATL. ACAD. SCI. (USA) (1992) Vol. 89, p. 3165-69.

(7) GROUPING OF CLAIMS

For purposes of this appeal, the claims 1-8, 10-14 and 16-35 are argued together as one group, and will stand or fall together.

(8) ARGUMENT

I. With Respect to Issue 1

Claims 1-8, 10-14 and 16-35 are were finally rejected under 35 U.S.C. § 103(a) as being obvious over United States Patent No.# 5,959,171 to Hyttinen *et al.*, in view of Rybak *et al.* As seen below, this rejection is, respectfully, improper and should be reversed.

The Final Rejection of the pending claims is inappropriate under the United States Supreme Court's guidance enunciated in the three-part test of Graham v. John Deere Company, 383 U.S. 1, 17, 148 U.S.P.Q. 459, 467 (1966). More to the point analysis of the instant claims leads to the conclusion that these claims are not obvious over the prior art references. *Graham* sets forth, the factual inquiries necessary to determine obviousness. These are as follows:

1. The scope and content of the prior art are to be determined;
2. The differences between the prior art and the claims at issue are to be ascertained; and
3. The level of ordinary skill in the pertinent art is to be resolved.

Graham directs that it is against this background that the obviousness issue is determined. Claims 1-8, 10-14 and 16-35 on appeal are directed to a method of producing an immunoglobulin-enzyme fusion protein in a transgenic animal production platform. This improvement utilizes a technically complex series of procedures and allows the recombinant production of a new class of molecule – an immunoglobulin-enzyme fusion protein. Moreover, the invention provided allows the transgenic production of such molecules in both a routine and more successful way.

In general, the method includes providing a transgenic animal, e.g., preferably a goat or a cow, which includes a transgene that provides for the expression of the biologically active fusion protein. That is, the production of a physiologically active immunoglobulin-enzyme fusion protein. Thereafter recovering the secreted immuno-fusion protein from the milk of the transgenic animal.

As the prior art amply demonstrates there are a growing number of recombinant proteins are being developed for therapeutic and diagnostic applications. However, many of these proteins may be difficult or expensive to produce in a functional form and/or in useful quantities using alternate methods, such as *in vitro* cell culture. Alternate and inferior methods of producing desirable immunoglobulin fusion molecules involve inserting the gene responsible for the production of a particular protein into host cells such as bacteria, yeast, or mammalian cells, and then growing the cells in *in vitro* culture conditions to produce the molecule of interest. In terms of collection or harvest, these modified cells must either be lysed or a worker in the field must collect the supernatant for cell culture systems that can secret a molecule of interest, with purification following this collection step.

It is important to note that traditional mammalian, bacteria or yeast cell culture systems may simply be unable to produce many complex proteins in a functional secreted form. While mammalian cells can reproduce complex proteins, they are generally difficult and expensive to grow, and often produce only nanogram per Liter quantities of protein. These low levels of production are simply commercially unacceptable. However, the transgenic production platform utilized by the Appellants in conjunction with the other discoveries included in the instant specification allowed the Appellants to reach the much higher production levels seen in transgenic animals. The limitations seen when using bacterial, yeast or mammalian systems, particularly with regard to complex proteins, such as immunoglobulin-enzyme fusion proteins, that require proper post-translational modifications and assembly to be in functional form, are thus overcome by the instant invention. Taken together, the improvement represented by the instant invention will allow therapeutic and commercial applications to go forward that otherwise would not be technically possible and/or commercially feasible.

A. HYTINNEN *ET AL.* TEACHES AWAY FROM THE CLAIMED INVENTION

The present invention claims a multi-faceted system of expressing an active immunotoxin active enzyme linked to an immunoglobulin or fragment capable of "targeting" the composition to a desired tissue type or receptor, and biologically active

variants thereof in the milk of transgenic animals. The disclosure of the current specification then overcomes a host of expression problems experienced with prior methods including without limitation; physiological reactions that are initiated by the nature of the wild type nucleic acid sequence itself; and/or those problems inherent with the production of active molecules within genetically modified animals. With regard to the Hytinnen *et al.*, reference the Examiner considers it as a reference that discloses an expression vector system analogous to that claimed in the instant invention. (Final Rejection of 6/20/02; pages 5-6). As discussed above, the expression system of the current claims focuses on transgenic animals and was developed to overcome not only the problems that transgenic animals have with the expression of a active enzymes and/or immunotoxins but to overcome the structural and sequence problems that mammalian cells may have in expressing certain nucleic acid constructs generally. This while Hytinnen teaches **away from confronting these difficulties** and instead uses a transgenic animal production platform to produce inactive molecules. These inactive molecules are later available for activation. (Col. 2 lines 50-60, Hytinnen *et al.*).

Specifically, Hyttinen *et al.* disclose producing a fusion protein in inactive form in the milk of a transgenic animal. Specifically, Hyttinen *et al.* disclose that there can be "severe side effects" when "producing potent polypeptides like growth factors, cytokines or enzymes" in the milk of transgenic mammals. (Col. 2 lines 23-24, Hytinnen *et al.*). To solve such problems, Hyttinen *et al.* disclose producing such polypeptides as part of a fusion protein such that the polypeptide is produced in the milk of the animal in inactive form. (emphasis added) (Col. 4 lines 52-54, Hytinnen *et al.*). Thus, it is clear that nothing in the Hyttinen *et al.* reference teaches or suggests producing a fusion protein which includes an enzyme, or an active immunoglobulin fusion protein, such that the enzyme is produced in the milk of a transgenic animal in active form. Therefore, nothing in the teachings of Hyttinen *et al.* could motivate a skilled artisan to produce fusion proteins in which the enzyme portion is in active form.. Rather, the Hyttinen *et al.* reference teaches the use of transgenic mammals to produce a less active or inactive protein as part of a fusion protein in milk. More to the point, Hyttinen *et al.* state that polypeptides (such as enzymes) are produced "as fusion proteins that are less active than said biologically active polypeptide in its free form, or non-active. The activity is diminished

or removed by having the biologically active polypeptide produced as a fusion protein" (column 2, lines 41-44, Hyttinen *et al.*). The claims recite the term "biologically" active form, and this expressly incorporates this important element and limitation into the claimed molecular construct of the intention – objectively taught against by Hytinnen et al.

It should be noted that the Appellants added the term "biologically active" to emphasize to the Examiner that nothing in Hyttinen *et al.* teaches or suggests that an enzyme produced as part of a fusion protein would be in its biologically active form. The focus in Hyttinen et al is to use the transgenic bioreactor to express a high level of inactive or less active protein since "[s]evere side effects are ... probable when producing potent polypeptides like growth factors, cytokines or enzymes.. ." ((column 2, lines 23-24, Hyttinen *et al.*); and see, (column 4, lines 51-55, Hyttinen *et al.*)). It is clear this is very different from the claimed invention which requires that the second member- the enzyme portion- of the fusion protein be produced in its biologically active form. Thus, unlike Hyttinen, the claimed first member does not reduce the activity of the second member of the fusion protein. Thus the teachings of Hyttinen *et al.* differ substantially from the instant claims. There is nothing in the Hyttinen *et al.* reference that would motivate a skilled artisan to produce fusion proteins in which the enzyme portion is in a biologically active state. In fact, it actually teaches that producing expression of a fully active enzyme portion is unfavorable.

Going further, despite the teachings of Hyttinen et al., directed toward the use of certain techniques that are designed to provide protection against the secretion of an active enzyme and any associated negative physiological effects seen in the transgenic animals used as "bioreactors" (i.e., and thereby objectively teaching away from the instant invention) Hytinnen et al., constitutes a failed experiment on its own terms. That is, mice used as an example of a productive "bioreactor" in Hytinnen et al., demonstrate very high hematocrit levels, when no active exogenous or transgenic erythropoietin was supposed to be in their systems due to the "protections" provided by the Hytinnen invention. The hematocrit levels that Hytinnen reports simply would not be seen absence of transgenically produced erythropoietin in their systems. (see, Example 3 (mouse line 115) as provided in Hytinnen et al., Figure 2, and claim 3). The important point for the purposes of this Appeal is that a

cited reference must disclose to the public an available way of making the product or achieving the result *successfully,* within the constraints of the technically possible and that allowable by law or regulation, if it is to properly remain grounds for a rejection based on obviousness – this Hytinnen *et al.*, does not do.

Therefore, as the United States Supreme Court has stated, "An inoperable invention or one which fails to achieve its intended result does not negative novelty." United States v. Adams, 383 U.S. 39 at 49-51 (1966); W.L. Gore & Assocs. v. Garlock, Inc., 721 F.2d 1540, 1549-50 (Fed. Cir. 1983). For this reason, failed experiments or inoperative inventions **cannot be considered prior art** sufficient to support an Examiner's rejection, be it one based on anticipation or obviousness. In re Wilder, 429 F.2d 447, 166 U.S.P.Q. 545 at 548 (C.C.P.A. 1970). Here, Hytinnen simply fails to provide any guidance or successful teaching that could lead to the current invention, rather it exemplifies the failures of the prior art. Accordingly, not only is there a difference between the prior art relied upon by the Examiner and the claimed invention, the prior art including Hytinnen *et al.*, such that the cited prior art either teaches away from the current invention or teaches a method or structure for altering an intended and realistic result in the current invention, and in so doing is ineligible to support an obviousness rejection.

Appellants therefore respectfully request the withdrawal of the Final Rejection of amended claims 1-8, 10-14 and 16-35 under 35 U.S.C. §103(a) as being unpatentable over Hyttinen et al (1994), in view of Ryback *et al.* (1992) and under 35 U.S.C. §103(a).

B. APPELLANT RECOGNIZES THAT THE LEVEL OF ORDINARY SKILLED IN THE ART IS HIGH

Applicant recognizes that the level of ordinary skill in the art is high. This is supported by the requirement of an understanding of the different abilities, strengths, weaknesses and effects of various protein expression systems, particularly with regard to transgenic animal expression systems. However, in light of the above, even given the relatively high standard of skill in the art, the clear lack of any teaching in any analogous art of applying solutions for the expression of immuno-fusion proteins in transgenic mammal expression systems requires a resolution of the *Graham* test with a finding of non-obviousness of the claims.

Moreover, as demonstrated by the level of skill in the art as shown by the Hytinnen patent, no one in the industry other than the Appellants has approached the problem of marrying the various requirements for utilizing a transgenic animal expression system for the production of immuno-fusion proteins in milk to answer the demonstrated need for a new class of therapeutic molecules. The novelty present in the current invention was taking an expression system design to an entirely new level than that performed and suggested by those skilled in the art, to arrive at a transgenic animal expression system proven to produce the needed immuno-fusion proteins for the treatment of a variety of diseases. The Appellants' invention is not merely the result of using a variety of molecular biology tools available to many researchers, rather it was the result of recognizing a long term problem, and inventing a solution to it, not approached or taught by the prior art. Given the above, Appellants respectfully request the withdrawal of the Final Rejection of claims 1-8, 10-14 and 16-35 under 35 U.S.C. §103(a).

C. RYBACK *ET AL.* IS NOT AN APPROPRIATE REFERENCE AND DOES DOT FALL WITHIN THE SCOPE OF THE APPLICABLE PRIOR ART

In the Final Rejection of June 20, 2002 the Examiner argued that "Therefore, in view of the benefits of using a transgenic bioreactor to produce large quantities of a protein for use in humans, it would have been *prima facie* obvious to the skilled artisan to express the fusion protein taught by Rybak *et al.* using the transgenic bioreactors taught by Hyttinen." (Final Rejection of June 20, 2002, page 5, 2nd paragraph). However, this ignores the activities of those skilled in the art at the time of this invention, and is contrary to the level of skill present in the art. The Examiner concedes that Hytinnen does not disclose and is in fact silent with regard to:

> does not discuss or provide any guidance with regard to the inclusion of any nucleic acid construct in the cells of a host transgenic mammal leading to the expression of a biologically active construct; and

fails to mention any teaching with regard to the expression or recovery of any immuno-fusion proteins from the milk of transgenic mammals.

Instead Ryback *et al.*, provides a primer on the production of DNA constructs in *Escherichia Coli* and the negligible production of a fusion protein in mammalian cell *in vitro* conditions. It should also be noted that Ryback is providing for the production of toxins only in an *in vitro* system and not the vastly more complex milieu of a live animal or specific tissues within that animal. It should be reiterated that the system of the invention is a transgenic living mammal, it is highly unlikely that anyone in the field of transgenics would look to a reference promoting the intracellular production and accumulation of toxins in transfectomas or related cell lines for guidance on how to allow or optimize the production of an active immunotoxin in a whole animal secretory expression system (see Ryback, Materials and Methods). In this light Ryback *et al.*, is simply non-analogous art incapable of supporting an obviousness rejection of the instant claims, or even making itself available for such a combination. There are simply no teachings to allow the methods of Ryback *et al.*, to make themselves available for an artisan in the field of transgenic mammals. Ryback *et al.*, fails to provide any discussion of any expression system other than *in vitro* cell culture conditions and in this way fails to understand or make obvious the true nature of the instant invention – the systematic use of a wide variety of molecular biology tools to overcome a panoply of expression problems for active immunotoxins in a transgenic animal system. Given this, the Ryback *et al.* reference is simply inapposite to the invention at hand and fails to provide a disclosure capable of sustaining an obviousness rejection of the instant claims alone or in any combination.

Moreover, the Rybak *et al.* reference discloses the production of a fusion protein consisting of an immunoglobulin heavy chain and angiogenin in a culture system. Rybak *et al.* disclose that this fusion protein is secreted into cell culture at extremely low levels, namely 1-5 ng/mL (0.00 1-0.005 mg/mL) based on the reactivity to anti-human IgG antibodies, and 1-2 ng/mL (0.001-0.002 mg/mL) based on angiogenin immunoreactivity. See column 5, lines 6-9. There is nothing in Rybak *et al.* which could thus teach or suggest that secretion of such a fusion protein could be improved or would in anyway approach the commercially acceptable levels needed to sustain the development of any

therapeutic composition. Thus, neither the Hyttinen *et al.* reference nor the Rybak *et al.* reference alone or in combination provide any indication of a likelihood of success in expressing reported poorly expressed protein in the milk of a transgenic mammal in which secretion is an essential step in recovering the fusion protein at levels as high as at least 0.1, 0.5 or 1 mg/mol (at least 100 times greater expression. In view of the extremely low expression levels of this fusion protein in cell culture (see, e.g., Rybak *et al.*), it would be unexpected that this fusion protein would be secreted at such high levels in the milk of transgenic mammals.

At best, the Ryback citation provides an *E. coli* platform for use in and with a variety of well known vectors including prokaryotes. However, it must be noted that in addition to the long list of deficiencies provided above it appears that the Examiner is treating the expression of a given target immuno-fusion protein in the milk of a transgenic animal as the expression of a target polypeptide in a vector along the lines of *E. coli,* in essence assuming they are identical in effectiveness and functionality. Respectfully, to do this is to fail to see the true parameters or importance of the instant invention. Appellants wanted to provide a means to reliably produce a protozoan protein that had resisted a multitude of previous scientific efforts at expression, including prokaryote expression. To do this Appellants purposefully employed a secretion system of incredible power and complexity (mammary epithelial cell lactation) that provides for the production and secretion of specific hormonally induced proteins (e.g., milk and milk proteins) in incredibly high concentration and pushes them out of the system of a whole animal in a regular reliable amount, in this way transgenic animals are quite unlike any other tool in the molecular biologists proverbial "tool kit." Ryback provides no guidance along this line, and is in fact, completely silent with regard to any differences in various expression systems. Moreover, along with the strength and peculiarities of transgenic mammals as "bio-reactors" the instant invention also provided solutions to a host of expression problems lamented in the prior art, but never overcome by it.

The invention of the Appellants required a systematic understanding of the host of problems seen before in the prior art and a novel way of using a variety of complex tools to produce the raw material for a new class of molecule produced in a novel way. Something which quite simply had not been done before, or reduced to practice. Prior to the elegant solution provided by the Appellants the common practice of those skilled in

the art was to attempt production of immuno-fusion proteins in an inactive form or to attempt expression at extremely low levels.

The Examiner's analysis thus inappropriately bases its rejection on the use of Ryback *et al.*, on the premise that one expression system and all of the interplay in the various tools used to achieve expression of a target protein or protein fragment is like another, and that therefore any cellular expression system with any given target protein is an appropriate and analogous prior art reference for the claimed invention of another such expression system. However, as the Federal Circuit has stated, "[t]wo criteria are relevant in determining whether prior art is analogous: (1) whether the art is from the same field of endeavor, regardless of the problem addressed, and (2) if the art is not within the same field of endeavor, whether it is still reasonably pertinent to a particular problem to be solved," Wang Laboratories, Inc. v. Toshiba Corp. 26 U.S.P.Q. 2d 1767, 1773 (Fed. Cir. 1993); *see also,* In re Clay, 23 U.S.P.Q. 2d 1058, 1060 (Fed. Cir. 1992); (The Wang court found that a prior art reference for using a nine bit controller consisting of nine memory chips encapsulated in ceramic dual in-line packages mounted on a circuit board substrate is not in the same field of endeavor as the claimed nine data memory chips for storing digital data on epoxy glass printed circuit board substrate merely because it relates to memories). Id. The Court further let stand a lower Court finding that the prior art reference was not analogous art and was not reasonably pertinent, i.e. the art would not logically have commended itself to an inventor's attention in considering his problem. Wang at 1773, and Clay at 1061.

The relevance of the Wang analysis to the instant matter lies in the fact that the Ryback reference is not only silent with regard to transgenic animals but rather focuses and provides teaching with regard only to simple expression in prokaryote expression vectors – essentially teaching away from the methods required to achieve success in the expression of immuno-fusion sequences in transgenic animals. Respectfully, the concerns for expression of immuno fusion protein sequences through plasmid vectors, typically in prokaryotes is an entirely different problem, with an entirely different set of concerns and hurdles preventing success than those inherent in the instant invention. (See Ryback, Discussion, and the Abstract). Thus, though Ryback might contemplate the use of similar sequences as those provided in the instant specification, the problem addressed and the solution provided by Ryback *et al.*, have little or nothing to do with the myriad of expression problems overcome by the instant claims, therefore falling outside the scope of appropriate art.

In a similar situation, the Federal Circuit concluded that as between a method and apparatus in which film is transferred to a welding station and a tape splicing machine capable of handling the same film, "[in] the light of all this evidence, one can reasonably conclude that the reference is not within the field of this inventor's endeavor and was not directly pertinent to a particular problem with which the inventor was involved." King Instrument Corp. v. Otari Corp., 226 U.S.P.Q. 402, 405 (Fed. Cir. 1985); *see also,* Union Carbide Corp. v. American Can Co., 220 U.S.P.Q. 584, 588 (Fed. Cir. 1984).

As in the King and Wang situations, the instant claimed invention is directed to features, methods and solutions of problems which are alien and non-analogous to the prior art cited by the Examiner. Therefore the teachings of Ryback *et al.*, are not pertinent to the claimed invention.

Accordingly, as in *Wang* and *King,* one must conclude that Ryback *et al.* is not within the field of this inventor's endeavor and is not pertinent in any way to the particular problems solved by the invention as provided in claims 1-8, 10-14 and 16-35. Appellants therefore respectfully request the withdrawal of the Final Rejection of amended claims 1-8, 10-14 and 16-35 under 35 U.S.C. §103(a) as being unpatentable over Hyttinen et al (1994), in view of Ryback *et al.* (1992) and under 35 U.S.C. §103(a).

II. SECONDARY CONSIDERATIONS INCLUDING LONG FELT NEED

A showing that an invention can satisfy a long felt need for a problem is relevant evidence of the non-obviousness and patentability of an invention. Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 1054-55 (Fed. Cir. 1988). To that end, it is important to note that the Appellants have developed a reliable production system for an anti-cancer immunoglobulin fusion molecule capable of specific targeting to cancerous epitopes of interest. A potential therapeutic where none existed previously.

To demonstrate the ongoing need for a production method of the type presented by the instant invention the Examiner is pointed at two short references present in the current art detailing the continuing need for a reliable immuno-fusion protein expression system, and more particularly for more efficacious novel cancer treatments. Frankel AE, et al., "*Anthrax Fusion Protein Therapy of Cancer*" CURR. PROTEIN PEPT. SCI. 2002 Aug;3(4):399-407; and, Nagy ZA, et al., "*Fully Human, HLA-DR-Specific Monoclonal*

Antibodies Efficiently Induce Programmed Death of Malignant Lymphoid Cells" NAT. MED. 2002 Aug;8(8):801-7 (Abstracts attached).

Given the above, Applicant's have demonstrated a long felt and ongoing need in the field for the development of a reliable expression system for expression of immuno-fusion proteins that is the focus of the current claims. This showing provides another *indicia* of the non-obviousness and patentability of the current claims. Appellants therefore respectfully request the withdrawal of the Final Rejection of amended claims 1-8, 10-14, and 16-35 under 35 U.S.C. §103(a).

III. THE EXAMINER FAILS TO MAKE OUT A CASE OF *PRIMA FACIE* OBVIOUSNESS

Establishment of a *prima facie* case of obviousness is a procedural tool for allocating the burden of proof as between an Applicant and the Examiner. The initial burden is upon the Examiner to present this *prima facie* case of obviousness to negative patentability. Respectfully, in the current case the Examiner has failed to establish the needed case of obviousness, thus without more the Applicant is entitled to a grant of the patent. In re Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

A *prima facie* case of obviousness is established when the teachings from the prior art itself suggest the claimed subject matter to a person of ordinary skill in the art. In re Bell, 991 F.2d. 781, 26 U.S.P.Q. 1529 (Fed. Cir. 1993); In re Rijckaert, 28 U.S.P.Q.2d 1955 (Fed. Cir. 1993). The basic considerations which apply to obviousness rejections under MPEP § 2141 are as follows:

(1) the claimed invention must be considered as a whole;
(2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
(3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and
(4) reasonable expectation of success is the standard by which obviousness is determined.

When the prior art itself fails to meet even one of the above criteria the cited art does not satisfy 35 U.S.C. § 103(a) and prevents the establishment of the required *prima facie* case of obviousness by the Examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992); In re Rijckaert, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). As pointed out above, the Hytinnen reference not only fails to render obvious the current claims it also fails to provide any incentive to combine with other prior art.

Moreover, if these failings are insufficient to disqualify the Hytinnen reference it should be noted that if the prior art methodology must be modified in any way to practice the instant invention the prior art citations must also render obvious these modifications or provide a reasonable expectation for the successful practice of the invention with the necessary modifications within the four corners of the references cited be the Examiner. In this case Hytinnen itself, as provided above fails to provide many of the fundamental elements of the current invention provides inaccurate guidance with regard to others, provides no suggestion of any combination with other art and, in fact, teaches away from the current invention. With these failures, the Hytinnen reference also fails to support any case of *prima facie* obviousness. *In re Oetiker*, at 1446. Thus, the pending claims cannot be obvious over Hytinnen *et al.* taken alone.

The difficulties associated with developing the instant invention, the long felt need for the invention and the flawed and incomplete methods of the workers in the field is discussed above and all underscore the novelty of the instant invention, but important here is that the combination of citations provided by the Examiner, especially with the flaws of the Hytinnen *et al.*, citation, prevent the establishment of any *prima facie* case by the Examine.

Ryback *et al.*, does not provide what Hytinnen *et al.*, lacks. As stated previously in response to the Examiners' use of Hytinnen *et al.*, this citation fails to provide any discussion or guidance with regard to a transgenic mammalian system, fails to discuss the methods of improving expression in those systems and fails to discuss or provide any teachings with regard to the expression of immuno-fusion proteins in the milk of transgenic mammals. Like Hytinnen *et al.*, discussed above, Ryback et al, provides no guidance with regard to the difficulties that can be experienced with protein expression when the sequences

of interest have several layers of problems that must be overcome to allow and/or optimize expression in a transgenic system. Moreover, Ryback *et al.*, does not attempt to suggest a combination with any other art. Therefore Ryback *et al.*, cannot negative or render obvious the instant claims taken alone, and provides no suggestion of combination with any other techniques to come close to the instant invention.

The Examiner asserts that the motivation to combine these references can be found in the discussion in Hyttinen *et al.* that "transgenic bioreactors. . .[express] large quantities of a protein for use in human." However, Hyttinen *et al.* provide no suggestion that a protein secreted at very low levels (i.e., less than 0.005 mg/mL) in cell culture could be produced in milk, a system requiring secretion signal sequences to work at any significant level, at any acceptable production level. The fact that Hyttinen *et al.* disclose using mammals "which produce large quantities of milk and have long lactation periods," provides absolutely no suggestion that the claimed fusion proteins, which were secreted so poorly in cell culture, could be secreted at levels of 0.1 mg/mL in milk. This was an unexpected result of the claimed invention.

Moreover, the Examiner's reliance on the Example provided in Hyttinen of an inactive EPO being produced as part of a fusion protein with ~-lactoglobulin, a native milk protein, still would not suggest that expression of non-native milk proteins, such as immunoglobulin fused to a non-milk enzyme provided in the currently claimed invention, would be successfully expressed at high levels. A native milk protein would be expected to be expressed at high levels in milk but there is no reason to expect that a protein not native to milk would be highly expressed in milk.

Thus, it is clear that neither the Hyttinen *et al.* reference nor the Rybak *et al.* reference, alone or in combination, teach or suggest the claimed invention. Moreover, there is nothing in either of these references that would motivate one skilled in the art to combine the teachings of these references to arrive at the claimed invention. Lastly, the expression levels of the fusion protein obtained in the milk of transgenic mammals, as presently claimed, would be unexpected in view of the very low expression levels of these proteins in other expression systems. Therefore, the Hyttinen *et al.* reference and the Rybak *et al.* reference do not render the claimed invention obvious.

In addition, it must be respectfully reiterated that each of the citations provided above fail to recognize, expressly or implicitly, any need, possibility or benefit of combining their disparate teachings in such a way that they might then read on the instant claims. Absent some teaching, suggestion, or incentive supporting this combination, a teaching that is simply not present in any of the citations provided by the Examiner, the references are incapable of supporting a obviousness rejection under § 103(a). Carella v. Starlight Archery, 231 U.S.P.Q. 644 (Fed. Cir. 1986).

Given this misreading of the requirements for patentability and the novel elements of the invention presented by the Appellants, it should also be pointed out that it is well settled law that there is no longer a "flash of genius" requirement for patentability. That is, patentability does not rest on the development of new technology that completely eliminates prior art problems and difficulties, rather, patents can and should be issued to stepwise improvements in technology that are novel and otherwise meet the standards of the Patent Code. Cuno Eng'g Corp. v. Automatic Devices Corp., 314 U.S. 84, at 91 (1941) (proclaiming the "flash of genius" standard later abolished by institution of the current United States Patent Code of 1952); Graham v. John Deere Co., 383 U.S. 1, at 15-16 (1966) (Specifically overruling Cuno) (as applied here, the complete inhibition of the myriad difficulties associated with the production of a biologically active immunotoxin/enzyme in a transgenic mammal production platform).

Respectfully, the Examiner must provide more than an odd pairing of references that recast some elements of known technology, and other elements that may hint at the novelty created by the Appellants in the instant invention. Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc. 231 F.3d 1339; 56 U.S.P.Q.2D 1641 (Fed. Cir. 2000). The Examiner must provide references that ***knowingly*** suggest the combination of protocols, tests, or principles, which will lead to the invention to be rendered obvious, and read upon its claims. The Examiner has not provided these references. Rather the Examiner has stated that the instant claims are "as a whole..*prima facie* obvious" (Final Rejection of June 20, 2002, page 5). Without more, this is a classic reproduction of the invention from improper hindsight, which cannot be used to negative patentability or establish the required case of *prima facie* obviousness. In re Dillon, 919 F.2d at 696, 16 USPQ2d at 1904 (Fed. Cir. 1990) (*en banc*); In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir.

1988); In re Geiger, 815 F.2d 686, 2 USPQ2d 1276, 1278 (Fed. Cir.1987). The art presented by the Examiner simply does not accomplish this task, not only because it art cannot be combined, but also because the citations relied upon by the Examiner teach away from the subject matter of the claims, whether taken together or separately.

Respectfully, it is thus the objective measure of obviousness that the prior art cited of record is incapable of supporting, thus preventing the maintenance of a 35 U.S.C. §103(a) rejection. Appellants therefore respectfully request the withdrawal of the Final Rejection of amended claims 1-8, 10-14 and 16-35 under 35 U.S.C. §103(a) as being unpatentable over Hyttinen et al (1994), in view of Ryback *et al.* (1992) and under 35 U.S.C. §103(a).

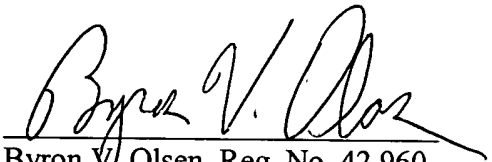
IV. CONCLUSION

Appellant respectfully submits that the prior art of record cannot objectively render obvious the instant claims or provide sufficient support for the maintenance of any *prima facie* obviousness rejection of the claims under 35 U.S.C. §103(a). Specifically, the prior art cited by the Examiner either teaches away from the current invention and/or is non-analogous art at variance with the teachings of the instant claims and specification. This then, respectfully requires a reversal of the Final Rejection issued by the Examiner.

Based upon the arguments made herein, the applicant requests that the Examiner's rejections of pending claims 1-8, 10-14 and 16-35 be reversed, and those said claims be allowed to go to issue.

Respectfully submitted,

Date: 10/23/03

By: 

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APPENDIX
BOARD OF PATENT APPEALS AND INTERFERENCE'S
APPEAL BRIEF

In re application of:	Michael D. Edge
Serial No:	09/398,610
Filed:	September 17, 1999
For:	TRANSGENICALLY PRODUCED PROTEINS
Art Unit:	1632
Examiner:	Anne Marie S. Wehbe
Attorney Docket Number:	GTC-42

The Claims on Appeal

1. (Amended) A method of making a transgenic fusion protein which includes a first member and a second member, wherein the second member is an enzyme, the method comprising: providing a non-human transgenic mammal which includes a transgene which provides for the expression of the fusion protein in the milk of the mammal; and allowing the transgene to be expressed, thereby providing the fusion protein in the milk of the mammal wherein the second member is in biologically active form and the fusion protein is produced at levels of at least about 0.1 mg/ml in the milk of the mammal.

2. (Reiterated) The method of claim 1, wherein the first member of the fusion protein is an immunoglobulin subunit.

3. (Reiterated) The method of claim 1, wherein the first member is fused to the second member and the first member includes a subunit of a targeting molecule and the second member encodes a cell toxin.

4. (Reiterated) The method of claim 1, wherein the first member includes a subunit of an inimunoglobulin specific for a tumor antigen.

5. (Reiterated) The method of claim 4, wherein the tumor antigen is from the group consisting of carcinoembryonic antigen (CEA), a transferrin receptor, TAG-72, and an epidermal growth factor.

6. (Reiterated) The method of claim 1, wherein the second member is an RNase.

7. (Reiterated) The method of claim 6, wherein the RNase is RNase A.

8. (Reiterated) The method of claim 1, wherein the second member is angiogenin.

10. (Reiterated) The method of claim 2, wherein the immunoglobulin subunit of the fusion protein is a human antibody or antigen binding portion thereof.

11. (Reiterated) The method of claim 1, wherein the fusion protein is produced in the milk of the mammal at concentrations of at least about 0.5 mg/ml.

12. (Reiterated) The method of claim 1, wherein the fusion protein is produced in the milk of a transgenic mammal at concentrations of at least about 1.0 mg/ml.

13. (Reiterated) The method of claim 2, wherein the immunoglobulin subunit of the fusion protein is a humanized antibody or antigen binding portion thereof.

14. (Reiterated) The method of claim 1, wherein the transgene encoding the fusion protein is a nucleic acid which comprises:

(a) a mammary epithelial specific promoter;

(b) a nucleotide sequence which encodes a signal sequence which can direct the secretion of the fusion protein;

(c) one or more nucleotide sequences which encode the fusion protein.

16. (Amended) A non-human transgenic mammal which includes a transgene that encodes a fusion protein, the transgene comprising: a mammary epithelial specific promoter, a nucleotide sequence which encodes a signal sequence which can direct the secretion of the fusion protein, and one or more nucleotide sequences encoding the fusion protein, wherein the fusion protein includes a first member and a second member, the second member is an enzyme produced in the milk of a transgenic mammal in biologically active form, and the fusion protein is produced in the milk of the transgenic mammal at a concentration of at least about 0.1 mg/ml.

17. (Reiterated) The transgenic mammal of claim 16, which can produce the fusion protein into its milk at concentrations of at least about 0.5 mg/ml.

18. (Reiterated) The method of claim 2, wherein the immunoglobulin subunit of the fusion protein is a chimeric antibody or antigen binding portion thereof.

19. (Reiterated) The method of claim 4, wherein the tumor antigen is a transferrin receptor.

20. (Reiterated) The method of claim 1, wherein the first member of the fusion protein is directly fused to the second member.

21. (Reiterated) The method of claim 1, wherein the first member of the fusion protein is linked to the second member by a linker sequence.

22. (Reiterated) The method of claim 1, wherein the transgenic mammal is a goat.

23. (Reiterated) The method of claim 1, wherein the transgenic mammal is a cow.

24. (Reiterated) The transgenic mammal of claim 16, wherein the first member of the fusion protein is an immunoglobulin subunit.

25. (Reiterated) The transgenic mammal of claim 16, wherein the first member is fused to the second member and the first member includes the subunit of a targeting molecule and the second member encodes a cell toxin.

26. (Reiterated) The transgenic mammal of claim 16, wherein the first member of the fusion protein includes a subunit of an immunoglobulin specific for a tumor antigen.

27. (Reiterated) The transgenic mammal of claim 26, wherein the tumor antigen is from the group consisting of carcinoembryonic antigen (CEA), a transferrin receptor, TAG-72, and an epidermal growth factor.

28. (Reiterated) The transgenic mammal of claim 16, wherein the second member of the fusion protein is an RNase.

29. (Reiterated) The transgenic mammal of claim 28, wherein the RNase is RNase A.

30. (Reiterated) The transgenic mammal of claim 16, wherein the second member of the fusion protein is angiogenin.

31. (Reiterated) The transgenic mammal of claim 24, wherein the immunoglobulin subunit of the fusion protein is a human antibody or antigen binding portion thereof.

32. (Reiterated) The transgenic mammal of claim 24, wherein the immunoglobulin subunit of the fusion protein is a humanized antibody or antigen binding portion thereof.

33. (Reiterated) The transgenic mammal of claim 24, wherein the immunoglobulin subunit of the fusion protein is a chimeric antibody or antigen binding portion thereof.

34. (Reiterated) The transgenic mammal of claim 16, wherein the mammal is a goat.

35. (Reiterated) The transgenic mammal of claim 16, wherein the mammal is a cow.

APPENDIX A